Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO)

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Abstract: The management of patients with brain metastases has become a major issue due to the increasing frequency and complexity of the diagnostic and therapeutic approaches. In 2014, the European Association of Neuro-Oncology (EANO) created a multidisciplinary Task Force to draw evidence-based guidelines for patients with brain metastases from solid tumors. Here, we present these guidelines, which provide a consensus review of evidence and recommendations for diagnosis by neuroimaging and neuropathology, staging, prognostic factors, and different treatment options. Specifically, we addressed options such as surgery, stereotactic radiosurgery/stereotactic fractionated radiotherapy, whole-brain radiotherapy, chemotherapy and targeted therapy (with particular attention to brain metastases from non-small cell lung cancer, melanoma and breast and renal cancer), and supportive care.

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Abstract

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Key Words

Brain Metastases, Neuroimaging, Neuropathology, Surgery, Stereotactic Radiosurgery / Stereotactic Fractionated Radiotherapy, Whole-Brain Radiation Therapy, Chemotherapy, Targeted Therapy, Supportive Care.

Running title: EANO Guidelines on Brain metastases

Importance of the Study

This manuscript reports the evidence-based guidelines on management of brain metastases developed by a multidisciplinary Task Force of the European Association of Neuro-Oncology (EANO), composed of medical experts from 10 European countries, including neurologists, neurosurgeons, radiation oncologists, medical oncologists, neuroradiologists and neuropathologists. These Guidelines should aid all professionals involved in the management

of patients with brain metastases in the daily clinical practice, and could also serve as a source of knowledge for institutions and insurance companies involved in cancer care in Europe.

Introduction

Brain metastases represent a common neurological complication of systemic cancer and are an important cause of morbidity and mortality.

Brain metastases are the most frequent intracranial tumors: the incidence of newly diagnosed brain metastases is 3-10 times the incidence of newly diagnosed primary malignant brain tumors[1]. The incidence of brain metastases has increased over time, as a result of increasing use of neuroimaging and improvement in the treatment of systemic disease.

The majority of patients who develop brain metastases have a limited life expectancy, as the appearance of the disease in the brain is frequently a hallmark of disseminated end stage disease, but patients with a limited disease may have a more favorable outcome with the use of intensive therapies. The knowledge of the most powerful prognostic factors (Karnofsky Performance Status- KPS, age, extracranial tumor activity, number of brain metastases, primary tumor type/molecular subtype) is crucial for predicting the individual prognosis. In this regard, several prognostic indices have been develop in order to distinguish subgroups of patient with different outcome [2,3].

The objective of this Guideline is to provide clinicians with evidence-based recommendations and consensus expert opinion for the management of adult patients with brain metastases from solid tumors.

The search strategy and selection criteria for reviewing the literature evidence can be found in the Table 1.

Diagnostic approach

Diagnosis by neuroimaging, Staging and Diagnostic neuropathology have been reviewed but not graded. These sections can be found in the Supplementary Material.

Treatment of newly diagnosed brain metastasis

Surgery

Three phase III trials have compared surgical resection followed by whole brain radiotherapy (WBRT) with WBRT alone in patients with in single brain metastases [4-6].

The first two studies, both of which were underpowered, reported a survival benefit for patients receiving the combined treatment (median survival 10 months vs 4-6 months). In the Patchell's study, patients who received surgery had a lower rate of brain relapses (20% versus 52%) and a longer time of functional independence. The third study, which included more patients with an active systemic disease (80% vs 30-40%) and a lower Karnofsky performance status, did not show benefit with the addition of surgery to WBRT [6]. However, a considerable fraction of patients assigned to WBRT alone actually crossed over to receive surgery, and this may have contributed to similar survival between the 2 treatment arms. None of the patients had pre-treatment MRI-scans, thus inclusion of patients with multiple brain metastases could not be excluded. Overall, the study was poorly designed and executed, making it less informative. In summary, there is limited class I evidence for survival benefit of surgical resection in addition to WBRT, and this is likely to be restricted to the subgroup of patients with controlled systemic disease and good performance status.

Surgical resection allows in the majority of patients an immediate relief of symptoms of intracranial hypertension, a reduction of focal neurological deficits and seizures, and a rapid steroid taper. Gross total resection of a brain metastasis can be achieved with lower morbidity using contemporary image guided systems, such as preoperative functional MRI, intraoperative neuronavigation and cortical mapping (class IV) [7]. An early postoperative MRI

has been reported to detect residual tumor in up to 20% of patients, and the presence of residual tumor has been associated with an increased risk of local recurrence (class IIIb) [8].

The impact of surgical techniques on the complication rate and functional outcome as well as on the risk of local relapse in patients with single brain metastasis has been recently reviewed (class IIIb) [9]. Leptomeningeal dissemination (LMD) can be a complication, especially in patients with posterior fossa metastases undergoing a "piecemeal" resection (13.8%) compared with "en bloc" resection (5% - 6%) (class IIIb) [10].

In patients with 2 or 3 brain metastases, who have a high performance status and controlled systemic disease, complete surgical resection yields results that are comparable to those obtained in single lesions (class IIIb) [11].

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) is a high precision localized irradiation given in one fraction using a combination of firm immobilization and image guidance. Convergence of multiple static or moving beams achieves a steep dose fall-off from the target to the surrounding normal structures allowing for a high dose to the tumor with low risk of damage to surrounding normal brain. Small brain metastases represent an ideal target for SRS, owing to the generally spherical shape, and distinct pathologic margins [12]. The dose is inversely related to tumor size. Maximal tolerated doses of SRS have been described in RTOG 9005 study [13], which included heterogeneous groups of patients with previously irradiated primary brain tumors and brain metastases. The suggested doses were 24 Gy for ≤ 20 mm, 18 Gy for 21-30 mm and 15 Gy for 31-40 mm in maximum diameter lesions. High single radiation doses to large tumours or tumours close to critical neural structures are associated with significant risk of toxicity, and there are attempts at employing hypofractionated regimens to achieve adequate local control with acceptable toxicity. However, randomized studies comparing stereotactic fractionated radiotherapy (SFRT) versus single dose SRS are lacking.

Single dose SRS in the treatment of a limited number (1-3) of newly diagnosed brain metastases has yielded a local control (defined as shrinkage or arrest of growth) at 1 year of 80%-90 % with symptoms improvement and median survival of 6-12 months (class IIIa) [14]. Patients with a single lesion, controlled extracranial disease and KPS of 70% or greater have longer survival [15,16]. Metastases from radioresistant tumors, such as melanoma and renal cell carcinoma, respond to SRS as do metastases from radiosensitive tumors [17]. Older patients (≥ 80 years of age) respond as well as younger patients [18]. The outcome following gamma-knife or linear accelerator (Linac)-based procedures is similar.

A randomized phase III study (RTOG 9508) in patients with 1-3 brain metastases, stratified by the RPA prognostic classification, investigated the value of the addition of a SRS boost to WBRT [19], and reported better local control and performance status at 6 months in the combined therapy group (class I) ; however, the survival advantage was only demonstrated in patients with single metastasis (6.5 months vs 4.9 months). A secondary analysis of RTOG 9508, that retrospectively stratified patients with the GPA prognostic classification, suggested that the addition of SRS to WBRT confers a significant survival benefit for patients with a good prognosis (GPA 3.5-4.0) regardless of whether they had 1, 2 or 3 brain metastases [20]. Conversely, this benefit did not extend to patients with lower GPA and/or 2-3 metastases..

In the past 5-10 years SRS has been increasingly used for patients with higher number of brain metastases, due to improved technology that allows the delivery of SRS with increasing speed while maintaining precision and accurancy. A prospective multicenter Japanese study investigated the use of SRS alone in 1194 patients with 1, 2 to 4 or 5 to 10 brain metastases, and found similar overall survival (10.8 months) and treatment related toxicity rates between the groups with 2 to 4 and 5 to 10 metastases (class IIIa) [16]. Cumulative volume of metastases, rather than the number, was reported as a significant prognostic factor [16].

Early, early delayed and late complications following radiosurgery are reported in 10-40% of patients, but serious complications are rare [21], although this may be a function of limited

follow up. Acute reactions presumed to be due to edema can occur within 2 weeks of treatment and consist of headache, nausea and vomiting, worsening of pre-existent neurological deficits and seizures. These reactions are generally reversible with steroids. Late complications (months to years) consist of hemorrhage and radionecrosis and have been reported in 1–17% of patients. Following SRS treatment-related change**s**, such as increase of contrast enhancement, necrosis, edema and mass effect on MRI are difficult to distinguish from tumor progression: in this regard, PET with FDG or amino acids, MRI perfusion and MR spectroscopy may provide additional information though are rarely diagnostic [22].

Radiation necrosis is commonly treated with steroids. Hyperbaric oxygen and/or the anti-VEGF agent bevacizumab, which may allow stabilization/normalization of the vascular permeability, can be useful in patients not responding to steroids [23]. Surgical resection **is** needed in some patients.

The risk of adverse radiation effects following SRS has been reported to increase with the increase of size of lesions with a 1 year cumulative incidence of 13-14% [24]. A wide range in the time of onset and time to improvement of these effects was observed.

There are no reports in the literature on the treatment of brain metastases with proton radiosurgery [25].

Surgery vs Stereotactic Radiosurgery

Most studies comparing surgery and SRS report similar outcomes: however, they are not randomized and likely to be affected by selection bias (class IIIb) [26,28].

SRS is considered less invasive, can be carried out in an outpatient setting, and is more cost-effective than surgery. ~~On the other hand,~~ Patients with larger lesions may require chronic steroid administration.

Whole Brain Radiotherapy following Surgery or Stereotactic Radiosurgery

There has been a long debate as to whether adjuvant WBRT, whose rationale is that of destroying microscopic disease at original tumor site or at distant intracranial locations, is

necessary after complete surgical resection or radiosurgery of a limited number of brain metastases [29,30].

Three large phase III trials [31-33] and a metanalysis [34] have been carried out. They demonstrated that the omission of WBRT in patients with a limited number of brain metastases after either complete surgery or SRS results in significantly worse local and distant control in the brain, but does not affect functionally independent and overall survival (class I). The American [31] and the Japanese [32] trials included patients with both stable and progressive systemic disease, while the European trial [33] was restricted to patients with stable systemic disease, i.e. those who could maximally benefit in terms of survival from improved intracranial control. A recent individual patient data meta-analysis of three randomized trials comparing SRS alone with SRS + WBRT in patients with 1 to 4 brain metastases [35] suggested a survival advantage for SRS alone in patients aged < 50 years without a reduction in the risk of new brain metastases with adjuvant WBRT; conversely, in patients aged > 50 years WBRT decreased the risk of new brain metastases but did not affect survival. A secondary analysis of the Japanese trial has retrospectively stratified patients by GPA score and suggested that a subgroup of patients with NSCLC with higher GPA scores (2.5-4.0) has a survival benefit from SRS+WBRT compared to SRS alone (median survival 16.7 vs 10.7 months) [36]. These are exploratory hypotheses, which require further studies.

Adjuvant WBRT following surgery reduces local and distant recurrences in the brain among patients with metastases > 3 cm and/or active systemic disease (class IIIb) [37].

The impact of adjuvant WBRT on cognitive functions and quality of life has been analyzed in few studies. Aoyama et al [38] compared the neurocognitive function of patients who underwent SRS alone or SRS + WBRT. More than 50% of patients experienced a significant improvement in MMSE score shortly after therapy (2-3 months) regardless of which treatment they had initially received, with subsequent deterioration of neurocognitive function in long-term survivors (up to 36 months) after WBRT. Chang et al [39] in a small randomized trial have

shown that patients treated with SRS plus WBRT were at greater risk of a decline in learning and memory function at 4 months after treatment compared with those receiving SRS alone.

A randomized phase III trial (Alliance trial) has compared SRS alone versus SRS + WBRT in patients with 1-3 brain metastases using a primary neurocognitive endpoint, defined as decline from baseline in any six cognitive tests at 3 months [40]. The decline was significantly more frequent after SRS + WBRT vs SRS alone (88% vs 61.9%) (class I) with more deterioration in immediate recall (31% vs 8%), delayed recall (51% vs 20%) and verbal fluency (19% vs 2%).

A quality of life analysis of the EORTC 22952-26001 trial has shown over 1 year of follow up no significant differences in the global Health Related Quality of Life, but patients undergoing adjuvant WBRT had transient lower physical functioning and cognitive functioning scores and more fatigue (class I) [41].

Based on the results of these trials, the American Society for Radiation Oncology (ASTRO) has recommended in their Choose Wisely campaign not to routinely add adjuvant WBRT to SRS for patients with limited number of brain metastases.

The issue of the need of WBRT following surgical resection is less well defined, as the randomized trials reported an increased risk of local relapse following surgery alone, though it remains unclear whether an active surveillance with salvage local therapy is as effective as an early additional treatment in the form of WBRT.

Stereotactic radiosurgery/Stereotactic fractionated radiotherapy following surgery

Postoperative SRS is an approach to decrease the local relapse following surgery, while avoiding the cognitive sequelae of WBRT. Several retrospective [42-44] and one prospective phase II trials [45] reported local control rates at 1 year around 80% (70%-90%) and a median survival of 10-17 months (class IIIa): this suggests that postoperative SRS is as effective as WBRT in achieving local control. An alternative approach is the use of stereotactic fractionated radiotherapy (SFRT) presumed to be associated with lower risk of radionecrosis in larger lesions [44,46].

The balance between risk and benefit is currently unknown with unsolved issues, such as the optimal dose and fractionation, the effects on survival, QoL, and cognitive funtion. Randomized trials are ongoing.

The risk of radionecrosis following postoperative SRS seems higher (9% - 17.5%) [47,48] than that reported by the EORTC study with WBRT following either surgery or radiosurgery (2.6%), and could increase over time (7% at 1 year and 16% at 2 years).

There is lack of information on the clinical counterparts of radionecrosis, and on the incidence of acute complications of SRS, such as seizures, headache and hemorrhage. One of the risks following SRS is the steroid dependency to control chronic edema: so far, both frequency and duration of steroid use following postoperative SRS have not been analyzed.

SRS to the resection cavity is associated with a risk of leptomeningeal relapse in 8% to 13% of patients [49,50], especially with breast histology (at 1 year 24% versus 9%): it is unknown whether the use of WBRT would decrease the risk of leptomeningeal relapse.

In conclusion, there is currenlty no high level of evidence in favour of SRS/SRT following surgery of brain metastases [51].

Whole-brain radiotherapy

Overall, in the different studies of the past a response following WBRT has been reported in up to 60% of patients; however, the neurological improvement could be partially attributable to steroids. Tumor volume reduction after WBRT has been associated with better neurocognitive function and prolonged survival [52]. Median survival following WBRT alone in patients with multiple brain metastases ranges from 3 to 6 months, with 10%-15% of patients alive at 1 year. A meta-analysis of 39 trials has concluded that altered WBRT dose fractionation schemes are not superior in terms of overall survival, neurologic function or symptom control as compared to standard fractionation (30 Gy in 10 fractions or 20 Gy in 5 fractions) (class I) [53]. A recent phase III non inferiority trial in patients with brain metastases

from NSCLC, not candidate to either surgery or radiosurgery, has not shown differences in overall survival and quality of life between WBRT and supportive care (class I) [54].

~~Up~~ To date, radiosensitizers have not provided any clear additional benefit over conventional radiotherapy.

Mild to severe cognitive dysfunctions occur following WBRT, and new approaches (neuroprotective drugs, new techniques of radiotherapy) are being developed in order to minimize the potential negative impact of WBRT.

In a randomized double-blind, placebo-controlled phase III trial (RTOG 0614) the use of memantine, a neuroprotective compund, during and after WBRT has resulted in better cognitive function over time, specifically delaying time to cognitive decline, and reducing the rates of decline in memory, executive function and processing speed (class IIa)[55]. Hippocampal avoidance WBRT (HAWBRT) using intensity modulated radiotherapy (IMRT) to reduce the radiation dose to the hippocampus[56] is not associated with increased risk of recurrence in the low dose region [57]. A single arm phase II trial (RTOG 0933) has suggested that the hippocampal avoidance may be associated with some sparing of WBRT-induced memory deficit and QoL (class IIb)[58], but these findings need confirmation in randomized trials currently underway.

Treatment of recurrent brain metastases

Reoperation has been suggested to yield a neurological improvement and prolongation of survival in patients with locally accessible brain relapse, high performance status, stable extracranial disease and relatively long time to recurrence (> 6 months) (class IIIb)[7]. Salvage SRS after WBRT has been widely used (class IIIb)[59-61]. In a large retrospective series [61] the median time to in-field and distant brain failure from salvage SRS were 14 months and 11.7 months, respectively, with a median time to CNS death of 9.31 months.

Reirradiation with SRS after local recurrence of an initial SRS has been employed in a limited number of patients, and the risk of long-term radionecrosis should be balanced against the potential but unproven clinical benefit [62].

Multiple courses of SRS for new brain metastases after an initial course of SRS with continue deferral of WBRT could yield high rates of local control, low risk of toxicity, and favorable duration of overall and neurologic progression-free survival [63]. A recent large retrospective series has reported that in patients undergoing multiple courses of SRS the aggregate volume, but not the cumulative number of brain metastases, and the GPA score, as recalculated at the second course of SRS, correlate with duration of survival (class IIIb) [64].

Chemotherapy and targeted therapies

General considerations

The level of evidence of studies on chemotherapy of brain metastases from solid tumors is class IIIa-b [65]. Response rates reflect the sensivity of the primary tumor: relatively high response rates in SCLC (30-80%), intermediate rates in breast cancer (30-50%) and NSCLC (10-30%), and low rates in melanoma (10-15%); response in the brain does not always parallel that at the extracranial sites; the response to chemotherapy from most chemosensitive tumors could be of the same order of that observed after radiotherapy.

The association of radiotherapy and chemotherapy may improve response rates compared with radiotherapy alone, but does not improve survival.

As for targeted therapies and immunotherapy, due to the increasing number of reports in the recent literature, the review and grading of evidence were restricted to clinical trials focused on brain metastases (mainly phase II trials).

Overall, the response rates of brain metastases to targeted agents in the different molecular subtypes seem higher than those observed after cytotoxic chemotherapy. However, the majority of targeted agents, that have been investigated so far, are small molecules, such as the

first-generation of tyrosine kinase inhibitors (TKTs), with a limited penetration of the blood-brain barrier (BBB), as they are substrates of active efflux transporters. Changing the schedule and/or regimen of administration (for instance pulsatile dosing of the EGFR inhibitor erlotinib) could increase the efficacy. Two factors limit the impact of the available targeted agents on brain metastases: an unpredictable lack of molecular concordance between the primary tumor and the brain metastases, and the rapid emergence of a secondary resistance, that can occur systemically but not necessarily in the CNS. To overcome all these limitations, several second- and third-generation small-molecule inhibitors are being investigated.

Last, there are numerous reports on the combination of immunotherapy and targeted therapies with SRS, but the literature on this issues is still too sparse [66,67]. In this regard, an increased risk of radionecrosis following SRS and immunotherapy has been suggested[68].

Brain metastases from NSCLC

Platinum compounds (cisplatin, carboplatin), alone or in combination with other agents (etoposide, vinorelbine, pemetrexed) are the most commonly used chemotherapeutics in the management of disseminated NSCLC, and have been employed in the setting of brain metastases, either upfront or at recurrence after radiotherapy[65]. The activity in terms of response rate is similar to that expected in the systemic setting, and is higher in chemonaive patients.

Targeted agents in patients with sensitizing EGFR and ALK mutations have shown activity. Response rates of brain metastases to EGFR TKI treatment (gefinitib, erlotinib, and afatinib) in patients with NSCLC harboring EGFR mutations reach 60%-80%, with rates of complete responses as high as 40%. Median OS is in the range of 15-20 months, and PFS in the brain is about 6.6 months-11.7 months, both significantly longer than for EGFR wild-type tumors[69].

Based on the high intracranial response rates TKIs alone have been proposed as initial treatment instead of WBRT in patients harboring activating EGFR mutations and

asymptomatic brain metastases[70-72], although this approach could be associated with a higher risk of subsequent intracranial relapse. The use of primary TKIs can avoid the adverse effects of WBRT although it is unlikely to avoid the need for subsequent WBRT. An alternative strategy is the use of cranial radiotherapy (SRS or WBRT) in combination with TKIs, which may improve PFS and OS compared with TKIs alone or radiotherapy with or without chemotherapy, although this is somewhat controversial and remains to be proven (class IIIa and b) [73,74]. A phase II study from China has resported that the combination of WBRT and erlotinib has a tolerable toxicities, and suggested a prolonged PFS and OS (class IIb) [75]. Conversely, phase II (class IIa and b) [76,77] and III (class I) [78] trials in patients with NSCLC brain metastases not enriched for EGFR mutations failed to demonstrate a superiority of the combination of erlotinib with either SRS or WBRT over radiotherapy alone with a suggestion of worse outcome in patients receiving the combined therapy. A Chinese phase II trial of WBRT with concurrent icotinib, another EGFR inhibitor, has suggested that the combination could improved survival compared with historical controls [79].

Other druggable alterations in NSCLC patients are the rearrangements of the "anaplastic lymphoma kinase" (ALK) gene, that seem to be constant between brain metastasis and primary tumor [80]. NSCLC with ALK activating translocations is sensitive to treatment with the ALK inhibitor crizotinib. In a retrospective analysis of the clinical trial PROFILE crizotinib has been associated with 55% intracranial control at 3 months of therapy in patients with ALK rearranged NSCLC, who were ALK inhibitor-naïve and had brain metastases [81]. Crizotinib yielded 18%-33% responses using RECIST criteria and the efficacy was observed among both radiotherapy-naïve and preirradiated patients (class IIIb). Responses are generally short-lived, and most patients need subsequent WBRT. Whether WBRT should be employed immediately after crizotinib response or after progression is still unclear. A recent multiinstitutional retrospective analysis has suggested that patients with brain metastases from ALK-rearranged NSCLC receiving radiotherapy (SRS and/or WBRT) and ALK inhibitors

(crizotinib, ceritinib, alectinib) have a prolonged overall survival (around 49.5 months) (class IIIb) [82].

Some efficacy with acceptable safety has been suggested in a phase II study of patients with asymptomatic untreated brain metastases from NSCLC with bevacizumab in combination with paclitaxel and carboplatin (class IIb) [83].

A recent early analysis of a phase II trial of the PD-1 inhibitor pembrolizumab has shown activity in untreated or previously irradiated brain metastases from NSCLC [84], but the trial is still ongoing.

Brain metastases from breast cancer

Chemotherapy regimens, variably combining capecitabine, cyclophosphamide, 5-FU, methotrexate, vincristine, cisplatin, etoposide, are active in patients with brain metastases from breast cancer [65].

The dual EGFR and HER-2 tyrosine kinase inhibitor lapatinib has shown modest activity in a phase II study in HER2+ breast cancer patients with brain metastases following trastuzumab-based systemic chemotherapy and WBRT (class IIb) [85]. CNS objective responses to lapatinib were observed in 6% of patients and 21% experienced ≥ 20% volumetric reduction in the CNS lesions. Another phase II single arm study (LANDSCAPE) has shown that the association of lapatinib and capecitabine in patients with radiotherapy-naïve brain metastases from HER-positive metastatic breast cancer yields durable responses in up to 65% of patients (class IIb)[86].

A single arm phase II trial on neratinib (HER2 TKI inhibitor) in patients with brain metastases, previously treated with either WBRT or SRS, has shown a response rate of 8% with an OS of 8.7 months (class IIb) [87].

Due to a lack of prospective trials, it is not clear whether trastuzumab, that probably can cross a more permeable BBB within established brain metastases, can be active as well [88]. Several case reports and small patient series indicate that the antibody-drug conjugate T-DM1 may be

active against brain metastases of HER 2-positive breast cancer (class IV) [89,90]. Few data only are available on the combination of different anti-HER 2 agents. There are no reliable data on the efficacy of endocrine therapies.

Brain metastases from melanoma

Fotemustine (response rate of 5-25%) and temozolomide (response rate 6-10%), either as single agent or in combination with WBRT, are active agents against brain metastases from melanoma[65,91].

Ipilimumab is a human monoclonal antibody directed against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), that potentiates the antitumor immune response. Despite the fact that ipilimumab does not cross the BBB, the activation of the immune system and the migration of lymphocytes into the brain allow an antitumor effect also in the brain parenchyma[92]. In a phase II study of ipilimumab in metastatic melanoma 12 of 115 patients had brain metastases at enrollment [93].Two of these patients achieved PR and three had stable disease (SD). Both patients with PR and one with SD had an overall survival of over 4 years. In a retrospective analysis of 38 patients with brain metastases treated within the French Expanded Access Program (EAP), 3 had PR and 5 SD, and 1-year survival was 10.5% [94]. An open-label, single-arm phase 2 trial included two cohorts of patients, 51 patients with asymptomatic brain metastases (cohort A) and 21 patients with symptomatic brain metastases controlled with corticosteroids (cohort B) (class IIb) [95]. Disease control (CR+PR+SD) after 12 weeks was 26 % in cohort A and 10 % in cohort B, with median OS of 7.0 months and 3.7 months, respectively. The response rates were similar for intra- and extracranial disease in both cohorts, and neurological toxicity was mainly of grade 1-2. A single arm phase 2 study, the NIBIT-M1-study, treated with ipilimumab and fotemustine 86 patients of whom 20 had asymptomatic brain metastases at baseline, mostly oligometastases [96]: 10 of these patients achieved disease control, and median PFS and OS were 4.5 months and 13.4 months,

respectively. In an Expanded Access Program (EAP) of stage 3 and 4 melanoma and asymptomatic brain metastastes failing or not tolerating other treatments [97], ipilimumab yielded a control rate of 27%, including 4 patients with a complete response and 13 with a partial response. Median progression-free survival and overall survival were 2.8 and 4.3 months, respectively, and approximately one-fifth of patients were alive 1 year after starting ipilimumab.

Chemotherapy [96] or radiotherapy [98] could induce a release of tumour antigens, thus increasing the antitumor activity of ipilimumab. An abscopal effect has been seen in melanoma patients, in whom radiotherapy for one lesion induced a shrinkage of non-irradiated lesions [99]. Sequence and timing of radiotherapy in relation to ipilimumab have not been fully elucidated[100,101]. To sum up, immunotherapy with ipilimumab has activity in brain metastases from melanoma, and the effect**s** seem similar in intra- and extracranial disease. In patients with symptomatic brain metastases, the effect is smaller, maybe due to the corticosteroid treatment or alternatively the general worse prognosis. An activity of PD-1 inhibitors, such as pembrolizumab or nivolumab, in brain metastases from melanoma has been suggested[84,102].

BRAF-mutations occur in approximately 50% of melanomas, resulting in a constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, and the BRAF mutation status is usually concordant betweent extracranial tumor and brain metastasis [103]. The BRAF-inhibitor vemurafenib has documented activity in brain metastases from BRAF-mutated melanomas [104]. An open-label pilot study included 24 patients with BRAF-mutated advanced melanoma and symptomatic brain metastases (class IIIa)[105]. All patients were on corticosteroids for symptom control, and had progressed after previous surgery or radiotherapy. Of 19 patients with measurable intracranial disease, 3 had a PR and 13 **a** stable disease. Median duration of response in the brain was 4.4 months with median OS of 5.3 months. In a retrospective review of 22 patients with asymptomatic brain metastases (class IIIb) [106] a 50% response rate was seen regardless of whether they had previous local therapy to

the brain or not, and clinical benefit was reported for two thirds of patients. Median time to progression (TTP) and median OS were 23 and 46 weeks for patients with objective response, and 12 weeks and 21 weeks for patients without objective response, respectively.

Two studies are available on the other BRAF inhibitor dabrafenib. A phase 1 study included 10 patients with asymptomatic, untreated brain metastases, and 9 achieved a decrease in the size of brain lesions and 4 achieved a CR (class IIIb) with a median PFS of 4.2 months [107].

The multicenter, open-label, phase 2 BREAK-MB trial enrolled 172 patients with asymptomatic, untreated (cohort A) or progressive (cohort B) brain metastases in melanoma patients with V600E or V600K mutation for treatment with dabrafenib (class IIb)[108]. Over 80% of patients in both cohorts with V600E mutations had intracranial disease control (CR+PR+SD), median PFS was longer than 16 weeks in both cohorts, and OS exceeded 31 weeks.The combination of BRAF inhibitors and SRS could improve survival [109,110], but an increase of toxicities could occur. A superior efficacy of copmbination therapies (BRAF and MEK inhibitors, nivolumab abd ipilimumab) is emerging in metastatic melanoma [111], but there are no data on brain metastases thus far.

Renal Cell Carcinoma

Some retrospective series have described responses of brain metastases to sunitinib [112,113] mostly in patients with small, asymptomatic metastases. In an opel label EAP sunitinib displayed a response rate of 12%, with PFS and OS of 5.6 months and 9.2 months, respectively (class IIIb) [112]. In another recent retrospective series on the efficacy of targeted therapies (sunitinib in 41 of 65 patients) a median OS of 12.2 months was observed (class IV)[114]. Conversely, in a small phase II study of 16 patients with untreated brain metastases

receiving sunitinib, 5 patients had SD only [115]. A synergism between targeted therapies and SRS has been suggested [116].

Supportive care: This section can be found in the Supplementary material.

Conclusion

Our Guidelines represent the state of knowledge at the time of writing. The European Association of Neuro-Oncology Website will provide future updates of these Guidelines.

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Table 1. Search strategy and selection criteria

- A Task Force was appointed in 2014 by the European Association of Neuro-Oncology (EANO) to draw Guidelines on the management of brain metastases from solid tumors. The Task Force was composed of medical experts from 10 European countries, including neurologists, neurosurgeons, radiation oncologists, medical oncologists, neuroradiologists and neuropathologists.
- References were identified through searches of PubMed, using specific and sensitive keywords, as well as combinations of keywords. Abstracts presented at American Society of Clinical Oncology in 2014 and 2015 were considered as well when relevant. When available we also collected existent guidelines from national multidisciplinary neuro-oncological societies. The final reference list was generated on the basis of originality and relevance to the scope of this review. The last update on PubMed was on July 15th, 2016.
- Scientific evidence was assessed and graded according to the following categories: class I evidence was derived from randomized phase 3 clinical trials; class IIa evidence derived from randomized phase 2 trials; class IIb evidence derived from single arm phase 2 trials; class IIIa evidence derived from prospective studies, including observational studies, cohort studies, and case-control studies; class IIIb evidence derived from retrospective studies; and class IV evidence derived from uncontrolled case series, case reports, and expert opinions.
- To establish recommendation levels, the following criteria were used: level A required at least one class I study or two consistent class IIa studies; level B required at least one class IIa study or several class IIb and III studies; level C required at least two consistent class III studies. When there was insufficient evidence to categorize recommendations in levels A-C we classified the recommendations as a Good Practice Point, if agreed by all members of the task force.

  When drawing recommendations, at any stage, the differences were resolved by discussions and, if persisting, were reported in the text.

Table 2. Recommendations at diagnosis

- When neurological symptoms and/or signs develop in a patient with known solid cancer, brain metastasis must always be suspected. (Good Practice Point).
- Contrast-enhanced MRI is the method of choice for assessment of brain metastases. A differential diagnosis between brain metastases and primary brain tumors (especially malignant gliomas and PCNSLs) and nonneoplastic conditions (abscesses, infections, vascular diseases) must be considered, even in patients with history of solid cancer and/or multiple lesions (Good Practice Point).
- Diffusion-weighted MR imaging is useful to differentiate among ring-enhancing lesions brain metastases from pyogenic abscesses (level C).
- Advanced neuroimaging techniques, such as MRI perfusion, MR spectroscopy, PET with FDG or amino acids, do not provide sufficient differentiation among enhancing lesions between brain metastases and other malignant brain tumors of glial or non-glial origin (Good Practice Point).
- In case of known primary tumor, systemic staging should include all the assessments required for the specific tumor type in order to define the activity of the primary lesion and the existence of extra cranial metastases (Good Practice Point).
- In case of unknown primary tumor a thorough physical examination (including testes and skin inspection), CT of the chest/abdomen, and mammography and/or ultrasound of breast are recommended and, if negative, whole body FDG PET is recommended (Good Practice Point).
- A tissue diagnosis is mandatory in patients with suspected brain metastasis on MRI and unknown primary tumor after a systemic workup before any treatment is undertaken (Good Practice Point).
- A tissue diagnosis should be considered in patients with well controlled systemic cancer when the neuroimaging appearance is atypical and/or a long interval has elapsed since the initial cancer diagnosis (Good Practice Point).

- Routine hematoxylin-eosin stain of the biopsy specimen usually is sufficient for a correct histological diagnosis. Immunohistochemical markers are required when the basic morphology is equivocal and/or the primary tumor is unknown in order to suggest the site of origin (Good Practice Point).
- Molecular markers that influence treatment decisions (predictive markers) should be assessed from brain metastasis tissue, if available, even when the respective marker(s) have already been assessed from tissue samples from extra-cranial tumor manifestations (Good Practice Point)
- CSF biochemistry and cytology are needed when a coexistent leptomeningeal involvement is suspected (Good Practice Point).
- Before treatment, patients should be assessed according to one of the existing prognostic scores (with preference for GPA score) (Good Practice Point).

Table 3. Recommendations regarding treatment of newly diagnosed brain metastases.

- Surgical resection should be considered in patients with a limited number (1 to 3) of newly diagnosed brain metastases, especially in case of lesions of ≥ 3 cm in diameter (symptomatic or not), lesions with necrotic or cystic appearance and edema/mass effect, lesions located in the posterior fossa with associated hydrocephalus, and lesions located in symptomatic eloquent areas (Good Practice Point).
- Surgical resection is recommended when the systemic disease is absent/controlled and the Karnofsky Performance score is 60 or more, as it can prolong survival (level A).
- Surgical resection can be an option when the systemic disease is active but effective systemic treatment options are available or when the primary tumor is relatively radioresistant (i.e. melanoma, renal carcinoma, colon carcinoma) (Good Practice Point).
- Stereotactic radiosurgery should be considered in patients with metastases of a diameter of ≤ 3-3.5 cm (level B).
- Stereotactic fractionated radiotherapy (SFRT) should be considered in patients with metastases larger than 3 cm in maximum diameter and a larger irradiation volume than 10 or 12 ccm due to increased toxicity and radiation necrosis of normal brain tissue (Good Practice Point).
- Stereotactic radiosurgery and/or stereotactic fractionated radiotherapy should be considered in patients with metastases that are not resectable due to location (i.e. basal ganglia, brain stem, eloquent cortical areas) or with comorbidities precluding surgery (i.e. older age, cardiovascular disease, etc) (Level C).
- When both surgical resection and SRS/SFRT are feasible, the choice should be made on a case-by-case basis with consideration given to tumor size, site, type of neurological symptoms, need for steroids, patient preference and/or physician expertise (Good Practice Point).

- Following complete surgical resection or SRS for a limited number of brain metastases, adjuvant WBRT is not unequivocally recommended due to lack of a survival advantage and risk of neurocognitive dysfunctions (level A).
- When withholding adjuvant WBRT following complete surgical resection or SRS, a close monitoring with MRI (every 3-4 months) is recommended (Good Practice Point).
- When withholding adjuvant WBRT after surgical resection of brain metastases postoperative stereotactic radiosurgery or stereotactic frationated radiotherapy to the resection cavity should be given to maintain and increase local control (Level C). As the post-resection cavity volume is usually smaller than pre-resection metastasis volume, it is recommended to perform a postoperative dedicated brain MRI for the SRS/SFRT, while the timing appears not to be relevant (Good Practice Point).
- When employing initial WBRT, a monitoring of cognitive functions with specific batteries is recommended (Good Practice Point).
- The decision regarding whether to employ SRS, SFRT, WBRT, alone or in combination, for patients with multiple brain metastases comes down to clinical discretion, patient preference and logistical considerations with the absolute number of brain metastases becoming less crucial (Good Practice Point).
- WBRT or best supportive care should be considered for patients with short life expectancy (low KPS score and/or progressive systemic disease) (level B).

Table 4. Recommendations regarding treatment of recurrent brain metastasis

- Surgery can be an option in selected patients with favorable prognostic factors (younger age, high performance status, controlled systemic disease) and accessible location or when a differential diagnosis between tumor regrowth and radionecrosis (especially following SRS) is required (level C).
- Salvage SRS following initial WBRT can be an option in terms of local tumor control and survival (level C).
- Multiple courses of SRS for new brain metastases after an initial course of SRS can represent an alternative to WBRT (level C).

Table 5. Recommendations regarding medical therapy

- Conventional chemotherapy may be the initial treatment for patients with brain metastases from chemosensitive tumors, like SCLC or breast cancer, especially when small and/or asymptomatic (Good Practice Point).
- No targeted agents are currently registered for the treatment of brain metastases from any solid tumors (Good Pratice Point).
- Patients with brain metastases from NSCLC harboring activating EGFR mutations or ALK rearrangements can derive benefit from the use of specific TKIs inhibitors (level C).
- Continuous HER2 blockade should be offered to patients with CNS metastases of HER2 positive breast cancer (Good Practice Point).
- Patients with brain metastases from HER2 positive breast cancer can derive benefit from the use of lapatinib, alone or associated with capecitabine (level C).
- Patients with melanoma and brain metastases can derive benefit from targeted agents either ipilimumab or BRAF inhibitors (level C).
- Patients with renal cell carcinoma and brain metastases can derive benefit from multitarget TKIs, in particular sunitinib (Good Pratice Point).
- Overall, while SRS or WBRT remain the mainstay of initial therapy, in selected patients with asymptomatic and small brain metastases targeted agents may be a reasonable option for an upfront treatment (Good Practice Point).
- Ultimately, patients with solid tumors and brain metastases should be encouraged to participate into clinical trials with targeted agents, when available (Good Practice Point).
- Pausing of treatment with a novel systemic agents during radiotherapy to the brain should be considered to minimize the risk of unexpected toxicities (Good Practice Point)

Table 6. Recommendations regarding supportive care

- For symptomatic patients dexamethasone is the corticosteroid of choice and a twice-daily dosing is sufficient. Total daily doses range between 4 mg and 32 mg (Good Practice Point).
- An attempt to reduce the dose of steroids in order to minimize side effects from chronic steroids administration, should be undertaken once the maximum neurological improvement has been obtained (Good Practice Point).
- Asymptomatic patients do not need steroids, while steroids may reduce the acute or subacute side effects of WBRT or SRS (Good Practice Point).
- Anticonvulsants should not be prescribed prophylactically (level A).
- In patients who suffer from seizures and need a concomitant treatment with chemotherapeutics or targeted agents, enzyme-inducing antiepileptic drugs should be avoided (level B).
- In patients with venous-thrombo-embolism (VTE), low-molecular-weight-heparin (LMWH) is effective and well tolerated for both initial therapy and secondary prophylaxis (level A). A duration ranging from 3 to 6 months is recommended for the anticoagulant treatment (Good Practice Point); however, there are some data supporting longer use in patient with active malignancies and those with recurrence despite therapy. Prophylaxis in patients undergoing surgery is recommended (level B recommendation).
- Bevacizumab treatment can be considered for symptomatic radionecrosis (Good Practice Point).

SUPPLEMENTARY MATERIAL

Diagnosis by neuroimaging

Contrast-enhanced MRI is more sensitive than enhanced CT (including double-dose delayed contrast) or unenhanced MRI in detecting brain metastases, particularly lesions in the posterior fossa or multiple punctate metastases [1,2]. Although T2-weighted and FLAIR images are sensitive in showing vasogenic edema as areas of increased signal intensity, not all metastatic lesions have sufficient edema to be identified.

There are no specific features on MRI that distinguish brain metastases; however, a peripheral location, spherical shape, ring enhancement with prominent peritumoral edema and multiple lesions all suggest metastatic disease a restricted diffusion in abscesses compared to unrestricted diffusion in necrotic glioblastomas or metastases, but the findings are not specific [3-5]. When employing MR perfusion imaging there is a tendency of lower cerebral blood volume values within the peritumoral region in brain metastases compared with glioblastomas [6,7]. MR spectroscopy in the peritumoral region more often shows a cholin to creatinin ratio lower in brain metastases compared with high grade gliomas[8,9]. FDG PET and 18F-FET PET do not provide sufficient differentiation between metastases and high grade glial tumors [10,11].

Staging

When a brain mass is suspected to be a brain metastasis but there is not a prior history of cancer, it is not clear how far to pursue the systemic investigation. As in most cases the primary tumor is located in the lung [12,13], a chest CT is always recommended. CT of the abdomen occasionally shows an unsuspected cancer. Further search for a primary tumor is almost never fruitful without positive features in the patient's history or localizing signs on the physical examination to suggest a specific

primary site [14]. Whole-body fluorodeoxyglucose (FDG) PET is a sensitive tool for detecting a "probable" primary tumor by visualizing foci of abnormal uptake, more often in the lung [15], but the specificity in differentiating malignant tumors from benign or inflammatory lesions is relatively low. Regarding brain metastases from an undetected primary site after the first staging, it has been shown that, when performing serial CT of thorax during the follow-up in asymptomatic patients, the primary tumor in the lung (a non small-cell carcinoma in the majority) may be discovered in almost all patients, but few of them ~~only~~ benefit in terms of survival from an early detection and treatment [16]. Therefore, a costly extensive evaluation for the undetected primary during the follow-up is not appropriate until more effective cancer therapies are available [14,16].

Diagnostic neuropathology

Cerebral metastasis of known primary tumors

In the situation of a patient with a known primary tumor, the histology and the marker profile of the primary and the cerebral metastasis will usually show similarities. However, the histologic comparison between the specimen of primary tumor and cerebral metastasis is important, as not infrequently patients may suffer from more than one tumor, and the metastasis may have originated from another primary than supposed.

Cerebral metastasis of unknown primary tumors.

For the determination of the lineage of the metastatic tumor, basic morphology will provide a first differentiation between carcinomas, lymphomas or melanomas. In addition, immunohistochemical profiles of metastases may be indicative of the site and lineage of the primary tumor [17]; however, they show variable overlap, and most markers are not specific. In case of a cerebral adenocarcinoma of unknown primary TTF-1 positivity is strongly associated with lung cancer and cancer of the thyroid. Negativity for CK7 and positivity for CK20 hints to colorectal cancer. Neuro-

endocrine differentiation is tested by chromogranin, synaptophysin and antibodies directed against specific hormones (insulin, gastrin, glucagon, serotonin and somatostatin). Further, there are immunohistochemical panels for mesenchymal tumors (vimentin, desmin, S100).

Attempts to identify unknown primary tumors from their metastases by using RNA expression profiles are ongoing. In general, few studies have focused on the comparison of primary tumors and their cerebral metastases with respect to lineage markers and biomarkers for treatment eligibility[18,19].

Recent studies have emphasized the genetic and phenotypic heterogeneity in cancer metastases and its impact on targeted therapies resistance [20,21]. The interest of the molecular characterization of brain metastatic disease is to document a potential phenotypic heterogeneity that could assist physicians in defining the therapeutic strategy. Indeed, biological documentation of metastatic disease is an approach that can lead to a change of the cerebral local treatment, but also to change the systemic treatment strategy [22].

Supportive care

Two evidence-based guidelines on the role of steroids to control vasogenic edema and mass effect in brain metastases are available in Europe [23] and US [24]. Dexamethasone is the steroid of choice because its minimal mineralocorticoid effect and long half-life, although any other corticosteroid can be effective if given in equipotent doses. A neurological improvement within 24-72 h after beginning of treatment is to be expected in up to 75% of patients with a dose effect relationship [25].

The need for anticonvulsant medication is clear in patients who have experienced a seizure while the evidence does not support prophylaxis with antiepileptic drugs (AEDs) in patients with brain tumors, including metastases. Twelve studies, either randomized trials or cohort studies, investigating the ability of prophylactic AEDs (phenytoin, phenobarbital, valproic acid) to prevent

the first seizure, have been examined, and none have demonstrated efficacy (class I) [26]. Subtherapeutic levels of anticonvulsants were extremely common and the severity of side effects appeared to be higher (20–40%) in brain tumor patients than in the general population receiving anticonvulsants, probably because of drug interactions. Phenytoin, phenobarbital, carbamazepine and oxcarbazepine stimulate the cytochrome P450 system and accelerate the metabolism of corticosteroids and antineoplastic agents, such as nitrosoureas, paclitaxel, cyclophosphamide, topotecan, irinotecan, thiotepa, adriamycin, methotrexate, imatinib, gefitinib, erlotinib and other tyrosine kinase inhibitors (TKIs), and thus reduce their efficacy. The role of prophylactic anticonvulsants remains to be addressed in some subgroups of patients who have a higher risk of developing seizures, such as those with metastatic melanoma, hemorrhagic lesions or multiple metastases. For patients who underwent a neurosurgical procedure the efficacy of prophylaxis has not been proven. The efficacy of novel AEDs (levetiracetam, topiramate, gabapentin, lamotrigine, lacosamide) has not been extensively investigated so far.

Anticoagulant therapy is the standard treatment for acute venous thromboembolism (VTE) in cancer patients. Subcutaneous low-molecular weight heparin (LMWH) is recommended for deep vein thrombosis and pulmonary embolism as well as for long-term secondary prophylaxis (class I) [27]. Anticoagulant therapy may increase the risk of intratumoral bleeding for brain metastases, especially for melanoma primaries. There are limited data on the use of novel oral anticoagulants [28].

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